CLAIMS

We claim:

1. A method for targeting and altering, by homologous recombination, a pre-selected target DNA sequence in a eukaryotic cell to make a targeted sequence modification, said method comprising introducing into at least one eukaryotic cell at least one recombinase and at least two single-stranded targeting polynucleotides which are substantially complementary to each other and each having a homology clamp that substantially corresponds to or is substantially complementary to a preselected target DNA sequence.

2. A method according to claim 1 further comprising identifying a target cell having a targeted DNA sequence modification at a preselected target DNA sequence.

3. A method according to claim 1, wherein said targeting polynucleotides are coated with said recombinase.

4. A method according to claim 1, wherein said eucaryotic cell is a plant cell.

5. A method according to claim 1, wherein said eucaryotic cell is a mammalian cell.

6. A method according to claim 1, wherein said eucaryotic cell is a zygote.

7. A method according to claim 1, wherein said eucaryotic cell is an embryonic stem cell.

8. A method according to claim 1, wherein said eucaryotic cell is an avian cell.

9. A method according to Claim 1, wherein said recombinase is a species of prokaryotic recombinase.

10. A method according to Claim 8, wherein said prokaryotic recombinase is a species of prokaryotic recA protein.

11. A method according to Claim 10, wherein said recA protein species is *E. coli* recA.

12. A method according to claim 1, wherein said recombinase is a species of eukaryotic recombinase.

13. A method according to claim 12, wherein said recombinase is a Rad51 recombinase.

14. A method according to claim 12, wherein said eukaryotic recombinase is a complex of recombinase proteins.

15. A method according to Claim 1, wherein said targeting polynucleotide is conjugated to a cell-uptake component.

16. A method according to Claim 15, wherein said cell-uptake component is conjugated to said targeting polynucleotide by noncovalent binding.

17. A method according to Claim 15, wherein the cell-uptake component comprises an asialoglycoprotein.

18. A method according to Claim 15, wherein the cell-uptake component comprises a protein-lipid complex.

19. A method according to Claim 15, wherein said targeting polynucleotide is conjugated to a cell-uptake component and to a recombinase, forming a cell targeting complex.

20. A method according to Claim 1, wherein the targeted sequence modification comprises a deletion of at least one additional nucleotide.

21. A method according to Claim 1, wherein the targeted sequence modification comprises the addition of at least one additional nucleotide.

22. A method according to claim 20 or 21, wherein said complementary single stranded targeting polynucleotides comprise an internal homology clamp.

23. A method according to claim 1, wherein the targeted sequence modification comprises the substitution of at least one nucleotide.

24. A method according to claim 23, wherein the targeted sequence modification comprises a plurality of substitutions.

25. A method according to Claim 1, wherein the targeted sequence modification corrects a disease allele in a cell.

26. A method according to Claim 25, wherein said cell is a human cell and the disease allele is a CFTR allele associated with cystic fibrosis.

27. A method according to Claim 25, wherein said cell is a mammalian cell and the disease allele is an OTC allele.

28. A method according to Claim 1, wherein the recombinase and the targeting polynucleotides are introduced simultaneously.

29. A method according to Claim 28, wherein the recombinase and the targeting polynucleotide are introduced into the target cell by a method selected from the group consisting of: microinjection, electroporation, laser poration, biolistics, or contacting of the cell with a lipid-protein-targeting polynucleotide complex.

30. A method according to Claim 1, wherein the targeted sequence modification creates a sequence that encodes a polypeptide having a biological activity.

31. A method according to Claim 30, wherein the biological activity is an enzymatic activity.

32. A method according to Claim 30 or 31, wherein the targeted sequence modification is in a human cell and encodes a human polypeptide.

33. A method according to Claim 32, wherein the targeted sequence modification is in a human oncogene or tumor suppressor gene sequence.

34. A method according to Claim 33, wherein the targeted sequence modification is in a human p53 sequence.

35. A method according to Claim 1, wherein each targeting polynucleotide comprises a homology clamp that is less than 1200 nucleotides long.

36. A method according to Claim 1, wherein the targeting polynucleotide is less than 1200 nucleotides long.

37. A method according to Claim 1, wherein the targeted sequence modification corrects a gene in a cell.

38. A method according to Claim 1, wherein the targeted sequence modification adds a gene to a cell.

39. A method according to Claim 1, wherein the targeted sequence modification disrupts a gene in a cell.

40. A method according to Claim 1, wherein the targeted sequence modification modifies a gene in a cell.

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41. A method according to claim 40, wherein the gene is the gal T gene associated with xenoreactivity in humans.

42. A method according to claim 1, wherein at least one of said complementary single stranded nucleic acids further comprise a chemical substituent.

43. A method according to claim 42, wherein said chemical substitutent is covalently attached to said nucleic acid.

44. A composition for producing a targeted modification of an endogenous DNA sequence, comprising two substantially complementary single-stranded targeting polynucleotides and at least one recombinase.

45. A composition according to Claim 44, further comprising a cell-uptake component.

46. A composition for producing a targeted sequence modification of a disease allele, comprising two substantially complementary single-stranded targeting polynucleotides, at least one of which contains a corrected sequence, and a recombinase.

47. A kit for therapy, monitoring, or prophylaxis of a gene comprising at least one recombinase and two substantially complementary single-stranded targeting polynucleotides.

48. A method for treating a disease of a animal harboring a disease allele, comprising administering to the animal a composition consisting essentially of two substantially complementary single-stranded targeting polynucleotides, at least one of which corrects the disease allele, and at least one recombinase.

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